The Actual Role of Therapy with Traditional Disease-modifying Antirheumatic Drugs in Psoriatic Arthritis

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ABSTRACT. Although several reviews and metaanalyses have shown lack of evidence of efficacy of traditional disease-modifying antirheumatic drugs (DMARD) in psoriatic arthritis (PsA), these drugs are very often used and are recommended by treatment guidelines around the world as first-line therapy for most patients with PsA. Some new investigations showed that higher doses of methotrexate (MTX) are more beneficial for patients with PsA with peripheral involvement. Also, observational studies have shown that retention of MTX for patients with PsA is comparable to that of patients with rheumatoid arthritis (RA), and that with MTX, remission is achievable by around 20% of patients with PsA. Sulfasalazine, leflunomide, and cyclosporine have also been shown to be effective in a small number of patients, although the overall effect on disease activity for these drugs is small. Although combination of anti-tumor necrosis factor agents with traditional DMARD is not mandatory in PsA as it is in RA, there is evidence that some extra benefit might be achieved when combinations are used, not only for the joints but for the skin. There is still room for the use of traditional DMARD in PsA, and for the time being, DMARD should still be considered as first-line therapy for most patients with PsA. (J Rheumatol 2012;39 Suppl 89:67–70; doi:10.3899/jrheum.120248)

Key Indexing Terms:
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Traditional disease-modifying antirheumatic drugs (DMARD) are used for the treatment of psoriatic arthritis (PsA) around the world. However, several reviews and metaananalyses have shown that there is a lack of evidence of the efficacy of these drugs in PsA[1,2,3]. What is the evidence for the use of traditional DMARD, and is there still a role for traditional DMARD in the treatment of PsA?

Table 1 summarizes the most important evidence-based guidelines published to date, including the recent ones from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis[4]. All these guidelines recommend the use of traditional DMARD as a first step for the treatment of peripheral involvement in PsA. The drugs suggested are sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF), and cyclosporine (CSA). Anti-tumor necrosis factor (TNF) agents are suggested only after traditional DMARD have failed, or as first-line therapy in predominant axial disease.

SSZ is the DMARD with the most evidence of efficacy in PsA. There are 6 randomized clinical trials (RCT) and 2 metaanalyses showing the efficacy of this drug. These studies, however, have shown statistically significant but clinically minimal effects of this DMARD in PsA[1,2]. For example, the effect size on tender and swollen joint counts of 2 of the largest trials showed values below 0.2 (Table 2)[1]. An effect size is the standardized mean difference between a treatment group and a control group for a given outcome. Effect size measurements tell us the relative magnitude of the experimental treatment (the size of the experimental effect). An effect size of 0.2 or less is considered small, meaning a slight effect on those outcomes compared with placebo.

Other DMARD recommended by all the guidelines is LEF[4]. There is 1 RCT evaluating LEF against placebo in 186 patients[5]. Patients' demographic characteristics were similar to those found in most of the RCT in PsA. Mean disease duration was 10 years and around half of the patients were DMARD-naive at study entry. Fifty-nine percent of patients taking LEF achieved composite outcome measurement (PsARC) response compared with 30% of the placebo group at 24 weeks. LEF was significantly better than placebo in all the outcome measurements assessed in the trial, including C-reactive protein (CRP) level response, Psoriasis Area and Severity Index (PASI) scores, and a dermatology quality-of-life questionnaire. Effect sizes for some of the outcomes are shown in Table 2, and were medium or small.

While there are no RCT comparing CSA to placebo, 3 published controlled trials have compared CSA to other DMARD[1]. The largest was that of Salvarani, *et al*, who performed a multicenter 24-week open trial comparing CsA (3

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Table 1. Summary of treatment recommendations in published evidence-based guidelines. Adapted from *International Journal of Clinical Rheumatology*, 2009;4:329-42, with permission of Future Medicine Ltd.

Guideline	Standard DMARD Therapy	Time to Failure (months)	Number of DMARD before Anti-TNF	Anti-TNF Without Previous DMARD	Time for Anti-TNF Failure
Canadian Rheumatology Association	SSZ, MTX	3	1	Yes, in predominant axial disease	16 weeks
British Society of Rheumatology	SSZ, MTX, CSA, LEF	6	2	No (axial disease not included)	3 months
French Society for Rheumatology	MTX, LEF, SSZ	4	1	Yes, in predominant axial disease	6–12 weeks
Italian Society for Rheumatology	MTX, CSA, SSZ, LEF	3	2	Yes, in predominant axial disease	3 months
American Academy of Dermatology	MTX, SSZ, LEF	Not stated	0–1	Yes, in severe disease	Not stated
GRAPPA	SSZ, LEF, MTX, CSA	3	1	Yes, in predominant axial or severe disease	Not stated

DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; SSZ: sulfasalazine; MTX: methotrexate; CSA; cyclosporine; LEF: leflunomide; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.

Table 2. Cohen's d effect size calculated on mean changes between baseline and final visit of selected outcome variables for different disease-modifying antirheumatic drugs in various studies. Negative values express an effect favouring placebo. Reproduced with permission from Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol 2006; 33:1422-30.

	SSZ		MTX	CSA	LPN	OG	IMG	AZA	INF	
	Combe and Gupta	Clegg	Willkens	Salvarani	Kaltwasser	Carette	Palii	Levy	Antoni	Antoni
Patients, n	117.23[†]	221	37	67	188	188	42	12	104**	200**
Followup, weeks	24+	36	12	24	24	24	24	26	16	16
Tender joint score	0.16	0.12	0.06	0.44	0.22	0.22	0.78	2.68	1.14[§]	1.14[§]
Swollen joint score	0.18*	0.02	0.02	0.46[#]	0.17	0.33	—	—	1.17[#]	0.81[#]
Pain (VAS)	0.36	—	—	0.53	—	3.64	–0.23	—	1.74	1.46
HAQ	—	—	—	—	0.29	—	—	—	0.87	1.17

AZA: azathioprine; CSA: cyclosporine; HAQ: Health Assessment Questionnaire; IMG: intramuscular gold; INF: infliximab; LFN: leflunomide; MTX: methotrexate; OG: oral gold; SSZ: sulfasalazine; VAS: visual analog scale. * Cohen's d effect calculated on final visit outcomes; [†] patients evaluated by Gupta, 1995; ** patients on drug and controls; [#] swollen joint count; [§] tender joint count.

mg/kg/day) with SSZ and symptomatic therapy [non-steroidal antiinflammatory drugs (NSAID), analgesics, and/or prednisone (5 mg/day)] in 99 patients with PsA[6]. The population in this study was slightly different – disease duration was shorter (around 2 years), and most of the patients had not received DMARD before. SSZ was not superior to symptomatic therapy in any of the outcomes assessed. CSA was significantly better than symptomatic therapy on American College of Rheumatology (ACR)50 and ACR70 response and better than SSZ on ACR70 response. As shown in Table 2, effect size was moderate for all the outcomes where it could be calculated. The major concern with CSA is its toxicity, and the fact that many rheumatologists are not familiar with its use.

The traditional DMARD more often used in the treatment of PsA around the world is probably MTX, as is shown in the study from Helliwell and Taylor from the population of patients included in the development of the CASPAR (ClASsification for Psoriatic ARthritis) criteria[7]. MTX was the traditional DMARD most frequently used as the first drug and in total received by 39% of the patients[7].

Surprisingly, there is less evidence about MTX than about other DMARD used in PsA. A review of the evidence of MTX has been recently published by Ceponis and Kavanaugh[8]. They found 5 RCT published to date. One showed significant improvement only in patient global assessment and percentage of psoriasis surface area.

More recently, Scarpa, *et al* published results of an RCT of patients with early PsA defined as oligo-entesoarthritis of < 12 weeks' duration[9]. Patients were randomized to NSAID alone or NSAID plus MTX for 3 months, and then all patients continued with MTX. Outcomes were assessed at 3 and 6 months. There was a significant improvement in joint count and acute-phase reactants in both groups at 3 months compared with baseline, and that improvement continued at 6 months. Patients randomized to MTX had a significantly better response on joint count at 3 months compared with patients taking NSAID alone, but the results were very sim-

ilar at 6 months after adding MTX to the other group. This study shows, although in a small group of patients, that in patients with early oligo-enthesoarthritis, the delay of 3 months in the beginning of treatment with MTX did not affect the outcome at 6 months[9]. There was no radiographic evaluation in this study. There is still doubt about whether this treatment delay might have had a deleterious effect on the outcome.

The MIPA (Methotrexate In Psoriatic Arthritis) study has recently been published[10]. Two hundred twenty-one patients were randomized to MTX or placebo in a 6-month RCT in which the primary outcome was the PsARC response. Only 65% and 69% of patients in the active and placebo groups, respectively, completed the trial. At 6 months there was significant improvement on the PsARC but not in the ACR20 response. There were no significant differences in any of the individual outcomes except for patient global and physician global assessments. The conclusion was that MTX, although it improved symptoms, had no effect on joint counts or acute-phase response. It was defined as a "symptom modifying agent" and not a DMARD[10].

Some evidence can also be obtained from observational studies. Chandran, *et al* published a reevaluation of the efficacy of MTX in their cohort of patients from Toronto, Canada[11]. They compared 59 patients seen between 1994 and 2004 with 19 seen between 1978 and 1993. There were some important differences between both cohorts: patients in the latest cohort had shorter disease duration (mean 8.5 vs 11.5 years) and received higher MTX doses (16.2 vs 10.8 mg/week). In the latter cohort, 68% of patients had 40% or greater reduction in joint count and they had less radiographic progression. The study suggested that treatment with MTX has changed in the past decade to include patients with shorter disease duration and less damage, at increased dose, and that there may be better response with less progression of damage[11].

Cantini, *et al* evaluated the frequency and duration of remission in patients with peripheral PsA treated with DMARD[11]. They used a stringent definition of remission, because all the following items needed to be fulfilled: fatigue (VAS 1-100 mm) < 10, pain (VAS 1-100 mm) < 10, articular morning stiffness (min) < 15, tender joint count 0, swollen joint count 0, normal erythrocyte sedimentation rate, normal CRP, absence of dactylitis, absence of enthesitis, absence of inflammatory spinal pain, and absence of extraarticular features. One hundred twenty-one patients were receiving MTX as monotherapy and 23 (19%) of them achieved remission with these strict criteria. Further, 34%, 23%, and 10% of those patients treated with MTX achieved ACR20, ACR50, and ACR70 response, respectively[12]. This study showed that remission was possible in a percentage of patients treated only with MTX.

Lie, *et al* compared the effectiveness and retention rate of MTX in PsA and RA from the Norwegian DMARD registry[13]. The study compared 430 PsA patients with a mean disease duration of 4.4 years with 1280 RA patients with similar disease duration. After 6 months of MTX treatment, both patients with PsA and those with RA improved in most disease activity measures and patient-reported outcomes. In the adjusted analysis, patients with PsA tended to have less improvement, but changes were in the same range as in patients with RA. An indirect way to evaluate the efficacy and toxicity of a therapy is retention of the drug. Two-year retention rates of MTX therapy in patients with PsA and RA were 65% and 66%, respectively[13]. This study showed slightly better results in patients with RA, but there was some good response in patients with PsA, and a similar retention rate at 2 years.

SSZ has strong evidence of efficacy with small effect on joint counts, MTX has less evidence and also small effect (although new studies with higher doses are showing better results), CSA has higher effect but is more toxic and less used in rheumatology, and LEF has good evidence but small effect. However, there are still around 20% to 40% of patients in whom a good response could be obtained with these traditional drugs. Because a short delay in the beginning of treatment with more effective drugs such as anti-TNF agents has not been proven to affect disease outcome and radiographic progression, a trial with traditional DMARD should probably be considered in most patients with PsA, as recommended in all the guidelines.

In RA the use of traditional DMARD as concomitant therapy with anti-TNF is mandatory. There is less evidence of the efficacy of this association in PsA. All clinical trials published to date of anti-TNF drugs in PsA included around 40% to 50% of patients taking MTX and continuing to receive it during the trial, independently of the group assigned by randomization. Gladman, *et al* compared the efficacy of adalimumab as monotherapy with adalimumab plus MTX[14]. They did not find differences in the arthritis efficacy measured by ACR20, ACR50, and ACR70 responses between patients with and without MTX. The only difference was in the skin response: PASI 75 scores were significantly better in patients in the combination group. Those patients who did not receive MTX had a significantly higher (37%) risk of discontinuation of anti-TNF treatment, suggesting that the concomitant use of MTX might improve anti-TNF retention over time[14]. Patients taking adalimumab had less radiographic progression than patients taking the placebo, independently of the concomitant use of MTX.

The STEREO trial was a prospective, 12-week, open-label, uncontrolled study in which patients received adalimumab 40 mg every other week in addition to standard therapy[15]. Of the 442 patients enrolled, 94% completed Week 12. One hundred forty-one patients received adalimumab monotherapy, and 197 received adalimumab combined only with MTX, 42 combined only with LEF, and 29 combined only with SSZ. Among the predictors of good clinical

response, the authors found that prior use of at least 2 DMARD and concomitant treatment with SSZ were associated with the achievement of a good European League Against Rheumatism (EULAR) response[15]. Although the number of patients with SSZ combined with adalimumab was small, the results suggest that this combination might be better than monotherapy with adalimumab to achieve good clinical response.

An interesting trial was performed in patients with only skin psoriasis. Patients were randomized to etanercept plus MTX that was tapered and stopped at 4 weeks or to etanercept plus continued MTX[16]. Patients' disease was very active and with a disease of very long duration. MTX dose was around 14 mg/week. A significantly higher proportion of patients in the etanercept/MTX continued arm was classified as clear or almost clear on the scale of physician global assessment of psoriasis (66.7 vs 37%), and significantly more patients achieved PASI 75 response at weeks 12 and 24 than patients in the etanercept/MTX tapered group. The study showed that the continuation of combined therapy with MTX plus etanercept was better than stopping MTX in this small group of patients with severe disease in spite of previous treatment with MTX.

The evidence of efficacy with traditional DMARD is scarce, the effect is small, and the evidence of effect on radiographic progression is even lower. However, some new information and observational studies suggest that between 10% to 40% of patients might have a good clinical response, and there is no evidence that a delay of 3 to 4 months in the initiation of more effective therapies would be harmful for most patients. There is no need to add traditional DMARD to anti-TNF therapy in all patients with PsA; however, combination therapy should be considered in patients with little or incomplete response. There is still room for the use of traditional DMARD in the treatment of PsA.

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